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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	28

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/438,358	GERARD ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-51,65-76 and 81-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-51,65-76 and 81-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 5/19/03 as Paper No. 27, in which several claims were amended (claims 14-15, 19, 31, 40 and 104). Claims 14-51, 65-76 and 81-104 are pending in the instant application.

Any rejection of record not addressed in the instant office action is withdrawn. This action is not final as there are new grounds of rejection made herein that were not necessitated by applicants' amendment of the claims in Paper No. 27.

Information Disclosure Statement

In Paper No. 27 applicants have requested the examiner's assistance in entering a series of references into the record corresponding to those listed on the IDS filed 9/18/00 as Paper No. 7, but not considered at that time because they were not present in the file. The examiner is in the process of attempting to obtain copies of each of the references. It would be helpful if applicants could fax to the examiner a new PTO-1449 referring to each of the references, without reference to all the already considered publications listed in Paper No. 7. Applicants' can fax such a document to the examiner directly at (703) 746-5114.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-36, 40-51, 73-76, 83-84 and 87-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection.**

Each of the claims is vague and indefinite in that the preamble of the claim recites a method for "enhancement of recombinational cloning" without an positive action step in the claim that refers back to the limitation of "enhancement". This makes it unclear as to the metes and bounds of "enhancing" recombinational cloning. Is it the addition of the recombinase or the ribosomal protein, or both, that is responsible for the "enhancement"? Or is some unrecited step required in order to achieve "enhancement"? In what way is the reaction "enhanced"? Does this refer in some way to improving the rate of cloning or the quality of the recombination products? It would be remedial to amend the claims to clearly indicate that the enhancement refers to the stimulation of recombinational cloning due to the addition of the ribosomal proteins.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-32, 36, 38-51, 65-72, 74-76, 87-89, 91-95, 98 and 100-103 are rejected under 35 U.S.C. 102(b) as being anticipated by Nash (Methods in Enzymology. Vol. 100, pp210-216, see the entire reference). **This rejection is maintained for reasons of (Paper Nos. 8, 13 & 25) and repeated below.**

Nash teaches the purification of the lambda Integrase (Int) protein and characterization of its activity throughout the purification process (e.g. Abstract; Table on page 214). The assay utilized to measure Integrase activity featured a linearized DNA bearing one Int recognition sequence and a supercoiled plasmid bearing a second Int recognition sequence (e.g. page 211, second paragraph-page 212, second paragraph). Recombination of the two DNA molecules produced a linear DNA having the "desirable" properties of being larger and possessing Int recognition sites attL and attR. Since Int was purified from E. coli cells after overexpression of Int from a plasmid bearing the int gene, it is inherent that the crude extracts used for the *in vitro* assay would include the E. coli ribosomal proteins, integration host factor (IHF), HU and the Int recombinase. Nash teaches the addition of crude preparations of IHF to *in vitro* recombination mixtures to enhance recombination (e.g. page 215, second full paragraph).

It is noted that Nash teaches the "isolation" of ribosomal and recombinase proteins to varying degrees for use in the recombination reaction mixtures throughout the reference. Nash also teaches the recombinant expression of the recombinase Int (e.g. pages 212-213, *Purification*). The newly added claim limitations regarding addition of BSA, spermidine, etc., to the reaction mixture can be found in the Materials and Methods section of Nash.

Response to Arguments/35 U.S.C 102 Rejections

Applicant's arguments filed in Paper No. 27 in regards to anticipation of many of the claims by the Nash reference have been fully considered but they are not persuasive. With regard to the Nash reference, the response essentially argues: 1) reiteration and reincorporation of all previous comments/arguments made against the rejection, 2) the claims are directed to

enhancement of recombinational cloning, and 3) Nash does not disclose that the methods disclosed therein provide any particular enhancement to cloning reactions.

All previous remarks and counterarguments presented by the examiner in the course of prosecution to date concerning the rejection of claims as anticipated by Nash are, where applicable, reiterated and incorporated here by reference. With regard to the limitation of "enhancement of recombinational cloning", it is first noted that this limitation appears only in the preamble of the claims and that there is no explicit linkage concerning the presence of the ribosomal proteins and any "enhanced recombination". Nash teaches each of the methods steps and specifically adds crude extracts from cells in order to provide IHF in order to improve the efficiency of recombination (e.g. page 215, second full paragraph). Alternatively, the "enhancement" could be considered to be due to the addition of the Int protein as opposed to reactions wherein Int was not added to the reaction mixture.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-51, 65-76, 81-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al in view of Nash (U) or Abremski et al (V) or Abremski et al(W). **This rejection is maintained for reasons of record (Paper Nos. 8, 13 & 25), which are repeated below.**

Hartley et al teach recombinational cloning methods which can be practiced *in vitro* and *in vivo* and which encompass each of the limitations of the instant claims (e.g. types of recombinases, DNA molecules used as substrates, Insert Donors, Vector Donors, etc.) (e.g. the Abstract; Figure 1; see the entire document).

Hartley et al do not teach the use of crude lysates comprising recombination factors in their *in vitro* methods. Hartley et al don't explicitly teach the addition of ribosomal proteins to their recombination reaction mixtures.

Nash teaches the purification of the lambda Integrase (Int) protein and characterization of its activity throughout the purification process (e.g. Abstract; Table on page 214). The assay utilized to measure Integrase activity featured a linearized DNA bearing one Int recognition sequence and a supercoiled plasmid bearing a second Int recognition sequence (e.g. page 211, second paragraph-page 212, second paragraph). Recombination of the two DNA molecules produced a linear DNA having the "desirable" properties of being larger and possessing Int recognition sites attL and attR. Since Int was purified from E. coli cells after overexpression of

Int from a plasmid bearing the int gene, it is inherent that the crude extracts used for the *in vitro* assay would include the E. coli ribosomal proteins, integration host factor (IHF), HU and the Int recombinase. Nash teaches the addition of crude preparations of IHF to *in vitro* recombination mixtures to enhance recombination (e.g. page 215, second full paragraph). It is noted that Nash teaches the "isolation" of ribosomal and recombinase proteins to varying degrees for use in the recombination reaction mixtures throughout the reference. Nash also teaches the recombinant expression of the recombinase Int (e.g. pages 212-213, *Purification*). The newly added claim limitations regarding addition of BSA, spermidine, etc., to the reaction mixture can be found in the Materials and Methods section of Nash.

Abremski et al (Journal of Biological Chemistry, 1984, Vol. 259, No. 3, pages 1509-1514; see the entire reference) and Abremski et al (Journal of Biological Chemistry, 1982, Vol. 257, No. 16, pages 9658-9662; see the entire document) teach the purification and characterization of the site-specific recombination enzymes Cre and Xis, respectively. Both references utilize a single recombinant vector comprising two recombination sites in an *in vitro* assay in which the products of recombination are two smaller, circular DNAs that can be cut with a single restriction enzyme and run on an agarose gel to assay formation of the different recombination products. In both instances, the enzymes were prepared from crude extracts of E. coli cells in which the enzymes were overexpressed and the enzymatic activity followed throughout the purification process (e.g. Table I of each paper). It is reasonable to expect that the E. coli ribosomal proteins as well as the E. coli proteins IHF and HU would have been present in each of the crude extracts tested.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use crude E. coli lysates comprising one or more of the recombination proteins in the methods taught by Hartley et al for recombinational cloning because 1) Hartley et al teach that their methods can be practiced *in vitro*, and because 2) Nash and the Abremski et al references teach that one can supply recombination proteins with crude extracts of E. coli cells comprising one or more recombination proteins for *in vitro* recombination reactions that effectively produce different recombination products. One would have been motivated to do so in order to receive the expected benefit of providing one or more recombination proteins without the need for further purification and, in the case of Int/Xis, providing multiple factors known to enhance recombination. Such extracts would be expected to also comprise the ribosomal proteins expressed in E. coli. Based on the entirety of the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a crude extract comprising one or more recombination proteins to practice the recombinational cloning methods taught by Hartley et al.

Response to Arguments/103 Rejection

Applicant's arguments filed in Paper No. 27 have been fully considered but they are not persuasive. Applicants' response essentially argues: 1) previous arguments against this rejection are reiterated and reincorporated in the response of Paper No. 27 by reference, 2) there is no suggestion or motivation to combine the teachings of Hartley et al with any of the cited references, 3) Hartley et al does not teach or suggest the use of crude extracts, and 4) it is

improper to consider what Hartley et al does not teach in making the rejection (i.e. Hartley et al does not teach that one cannot practice their methods with crude extracts).

All previous arguments of record presented by the examiner in response to applicants' remarks are hereby incorporated by reference and applied, where applicable, as before in this action. The examiner provided a rational for combining the teachings of Nash and the Abremski et al references that was not dependent upon any suggestion by Hartley et al to use crude extracts. This appears to be some sort of argument that either the Hartley et al teachings and claims don't encompass *in vitro* reactions using crude cell extracts to provide the recombination proteins, or that the teachings of the secondary references are not analogous art to the Hartley et al reference. The examiner's comment that Hartley et al does not teach that such crude extracts cannot be used was made in response to arguments that it is unclear why the examiner contends that the methods taught by Hartley et al encompass the use of crude cell extracts. One of skill in the art, aware of the pertinent art concerning *in vitro* site-specific recombination reactions would necessarily have been aware of the ability to use crude extracts of cells to provide essential recombination proteins to such *in vitro* recombination reactions, as evidenced by each of the cited secondary references. Absent any statement by Hartley et al that their invention is limited to highly purified preparations of recombination proteins, and in view of the state of the art, the skilled artisan would recognize that the methods taught by Hartley et al could be practiced with crude cell extracts and that the cited references are in fact analogous art. Applicants have not presented any argument that one could not have practiced the claimed methods with crude extracts, as taught by Nash and the Abremski et al references, or that one would not receive a benefit of not having to purify the recombination proteins.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-51, 65-76, 81-104 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37 of U.S. Patent No. 5,888,732 in view of Nash (U) or Abremski et al (V) or Abremski et al(W). Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons given below. **This is a new rejection.**

The instant claims are drawn to *in vitro* methods of recombinational cloning wherein ribosomal proteins are also included in the recombination mixture. The cited claims from the '732 patent are all directed to *in vitro* methods of recombinational cloning which, in view of the state of the art, would encompass the use of crude cellular extracts from E. coli to provide one or more recombination proteins to the *in vitro* recombination mixture. Such crude cell extracts would be expected to comprise one or more of the E. coli ribosomal proteins.

The teachings of Nash and the Abremski et al references are described above and are applied as before.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use crude E. coli lysates comprising one or more of the recombination proteins in the methods recited in the claims of Hartley et al for recombinational cloning because the recited claims encompass *in vitro* methods wherein crude extracts are used to provide the recombination proteins, and because the Nash and the Abremski et al references teach that one can supply recombination proteins with crude extracts of E. coli cells comprising one or more recombination proteins for *in vitro* recombination reactions that produce different recombination products. One would have been motivated to do so in order to receive the expected benefit of providing one or more recombination proteins without the need for further purification and, in the case of Int/Xis, providing multiple factors known to enhance recombination. Such extracts would be expected to also comprise the ribosomal proteins expressed in E. coli based upon the extract preparation steps taught by each of the secondary references. Based on the entirety of the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a crude extract comprising one or more recombination proteins to practice the recombinational cloning methods recited by the Hartley et al claims.

Response to Arguments/Obviousness Double Patenting

Applicant's arguments filed in Paper No. 27 to a similar rejection made without any secondary references have been fully considered. The rejection made above in view of the Nash and Abremski et al references addresses the argument concerning the lack of additional references concerning the use of crude cell extracts in *in vitro* recombination methods.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 746-5114.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
August 7, 2003